REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112 are respectfully requested in light of the remarks which follow.

At the outset, Applicants thank Examiners Stucker and Seharaseyon for granting and participating in the interview on August 27, 2002.

Support for the amendments to claims 1 and 2 can be found at least in the examples and original claims as-filed.

Without acquiescing to the rejections against claims 4, 8, 12, 16, 20, 24, 27, 31, 35, 39, 43, and 47, Applicants have canceled these claims without prejudice or disclaimer as to the subject matter contained therein in order to advance prosecution and expedite allowance. Applicants reserve the right to file a continuation or divisional application on the subject matter canceled by way of this amendment.

1. FINALITY OF RESTRICTION REQUIREMENT

The Office Action indicates that the restriction requirement has been made final.

2. TITLE

The title of the invention stands objected to for purportedly not being descriptive. Applicants have amended the title ("Use of Certain Metalloproteinase Inhibitors For Treating Nerve Disorders Mediated by Nucleus Pulposus" as amended), thereby mooting the objection. Support for the amendment can be found at least in the original title, page 2, line 12 and the original claims. Accordingly, Applicants respectfully request withdrawal of the objection.

3. SUBMITTED INFORMATION DISCLOSURE STATEMENTS

Applicants noted during the interview and for the record that not all of the Information Disclosure Statements (IDSs) which have been submitted to date have been acknowledged by the Office. Specifically the IDS submitted on August 7, 2001 remains

outstanding. Applicants respectfully request a copy of the acknowledged IDS with the next Office Action issued by the Office.

4. **REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Claims 27, 28, 31, 32, 35, 36, 39, 40, 43, 44, 47, and 48 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 27, 28, 31, 32, 35, 36, 39, 40, 43, 44, 47, and 48 stand rejected under 35 U.S.C. § 112, second paragraph, for the recitation of "pharmaceutical composition of claim 22" because claim 22 is purportedly drawn to a method. The claims were further rejected because no method steps were provided.

Claims 27, 31, 35, 39, 43 and 47 have been canceled by the instant amendment, thereby mooting the rejection as to these claims. Applicants have amended claim 28 to recite "claim 26", which is directed to a pharmaceutical composition. This amendment thereby obviates the rejections to claim 28 and its dependent claims (*i.e.*, claims 32, 36, 40, 44 and 48). Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 2, 26, 29, 30, 33, 34, 37, 38, 41, 42, 45, and 46 stand rejected under 35 U.S.C. § 112, second paragraph for the recitation of the term "pharmaceutically effective amount" because it is purportedly unclear what pharmaceutically effective amount is encompassed in the instant claim. Applicants respectfully traverse the rejection.

"Effective amount" or in this case "pharmaceutically effective amount" is a commonly recognized term of art. First, it is evident from the claims that the compositions are to be utilized for pharmaceutical purposes. Thus, the claim requires that the amount of the active agent(s) be effective for a pharmacological utility. *See, Ex parte Skuballa*, 12 U.S.P.Q.2d 1570, 1571 (Bd. Pat. App. & Int. 1989) ("As such, this claim requires that the amount of the active agent be effective for a pharmacological utility."). If this was not enough on its face, the claims when read in light of the specification clearly show that the effective amount is one necessary to treat nerve disorders mediated by nucleus pulposus. Therefore, the claims as written are definite. Applicants respectfully request withdrawal of the rejection in light of at least the above arguments.

5. **REJECTIONS UNDER 35 U.S.C. § 101**

Claims 27, 28, 31, 32, 35, 36, 39, 40, 43, 44, 47, and 48 stand rejected under 35 U.S.C. § 101 for the claimed recitation of a use, purportedly without setting forth any steps involved in the process. In view of the amendment to claim and 28 and the cancellation of claims Claims 27, 31, 35, 39, 43 and 47, the rejection under 35 U.S.C. § 101 is mooted and can be withdrawn.

6. **REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)**

Claims 1-48 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of nucleus pulposus-induced nerve root injury, purportedly does not reasonably provide enablement for treating nerve disorders. Given the breadth of claims 1 and 2 in light of the unpredictability of the art as determined by the purported lack of working examples, the level of skill of the artisan, and the purported lack of guidance provided in the instant specification and the prior art of record, it would purportedly require undue experimentation for one of ordinary skill in the art to make and use the claimed invention to treat all nerve disorders using the TNF-α inhibitors. Claims 3-48 stand rejected under 35 U.S.C. § 112, first paragraph, because they depend on rejected claims 1 and 2.

Applicants traverse the rejection. To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner ***must*** provide evidence or technical reasoning substantiating those doubts. *In re Wright*, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993); M.P.E.P. § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application ***must be*** considered enabling. *In re Wright*, at 1513.

Applicants initially notes that the nerve disorders to be treated are those which involve "nerve root injury" (*see,* at least page 2, lines 9-10). Thus, not ***all*** nerve disorders are contemplated for treatment using the compositions and methods claimed. However, Applicants have made this more evident with the amendments to claims 1 and 2. Applicants note that the amendments and discussion with regard to the specification was agreed upon

during the interview as overcoming the enablement rejection under 35 U.S.C. § 112, first paragraph.

For the record, Applicants further note that the Office Action states that "applicant has not provided examples of the efficacy of treating already established disease subjects or applicable model of nerve disorders with TNF-α inhibitors. . . ." (Office Action, page 5, lines 13-15). This is incorrect. First, Applicants are under no burden to provide any working examples. Absence of ***working examples***, prophetic or actual, in a specification is without significance, since examples are not necessary and even though a full example may provide added useful information, the test is whether an individual possessed of knowledge of one skilled in the art could practice invention without exercise of ***undue amount of experimentation***. *Ex parte Nardi & Simier*, 229 U.S.P.Q. 79, 80 (Bd. Pat. App. & Int. 1986) and M.P.E.P. § 2164.02. However, Applicants provide working examples including an example of a metalloproteinase inhibitor (*i.e.*, doxycycline).

Applicants turn the Examiner's attention to the experiments discussed in the application. Specifically, in Series 2, pigs were treated with 100 mg i.v. doxycycline (4/13 pigs), TNF-α antibody (5/13 pigs), and the remaining pigs remained untreated (control group). The results demonstrated that both the doxycycline and the anti-TNF-α antibody blocked the nucleus pulposus induced reduction of conduction velocity.

Finally, in the Series 3 experiment, Applicants demonstrate using a different antibody (*i.e.*, infliximab; Remicade®) and an inhibitor of the TNF receptor (*i.e.*, etanercept, Enbrel®) using the same *in vivo* animal model, that both agents blocked nucleus pulposus-induced reduction of conduction velocity (Specification, page 4, lines 13-15). Thus, in light of the above, Applicants clearly provide working examples using several different TNF-α inhibitory compounds, including a metalloproteinase inhibitor.

In light of the above amendments to the claims, arguments and in view of the agreement reached during the interview, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

7. **REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)**

Claims 1-48 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Without acquiescing to the arguments set forth in the Office Action and merely to further prosecution of the application, Applicants have amended claims 1 and 2 such that the claims are directed to "nerve disorders mediated by nucleus pulposus". Applicants maintain the right to pursue subject matter canceled by way of this amendment any divisional or continuation application on the canceled subject matter.

As immediately apparent, nerve disorders are discussed on at least pages 1-2 of the specification. From this discussion as well as the rest of the specification, it would be clearly evident to the skilled artisan as to what the term encompasses. Accordingly, in view of the amendments to the claims and agreement reached during the interview, the amended claims obviate the rejection under 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully request withdrawal of the rejection as to the remaining claims.

8. **REJECTIONS UNDER 35 U.S.C. § 102(a)**

Claim 1 stands rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Sommer *et al.* Sommer *et al.* purportedly teach the use of metalloproteinase inhibitor TAPI to block the mature TNF. The disclosure of Sommer *et al.* purportedly anticipates claim 1. The instant invention is directed to treatment of a nerve disorder by inhibiting TNF-α using metalloproteinase inhibitor. Claims 3-25, 27, 28, 31, 32, 35, 36, 39, 43, 44, 47, and 48 also stand rejected under 35 U.S.C. § 102(a) because they depend on rejected claim 1.

"Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claims". *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). Without acquiescing to the arguments set forth in the Office Action and merely to further prosecution of the application, Applicants have amended claims 1 and 2 such that the claims are directed to "nerve disorders mediated by nucleus pulposus". As amended, the claims are directed towards a method of or composition

for treating a nerve disorder mediated by nucleus pulposus in a mammal. As agreed during the interview, no where in the reference by Sommer *et al.* is there a teaching or a suggestion of such a method or composition. Thus, in view of the amendments to the claims and the above arguments above and the agreement reached at the interview, the claims as amended obviate the rejection under 35 U.S.C. § 102. Thus, Applicants respectfully request withdrawal of the rejection.

9. **REJECTIONS UNDER 35 U.S.C. § 103(a)**

A. Sommer in view of Xue

Claims 1-48 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Sommer *et al.* in view of Xue *et al.* (U.S. Patent No. 5,703,092). The Examiner asserts that one of ordinary skill in the art would have been motivated with reasonable expectation of success to modify the methods of Sommer *et al.* in view of Xue. Sommer *et al.* is cited for the reasons discussed *supra*. Xue *et al.* is asserted as disclosing "the identification of a metalloproteinase inhibitor which inhibits the production of TNF and thus is useful for the treatment of various diseases including inflammatory conditions (abstract)."

Applicants traverse the rejection. To establish a *prima facie* case, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine the reference. *See, In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See, Amgen, Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Many pitfalls exist that would eliminate a reasonable expectation of successfully obtaining a patent. Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See, In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Also, the teachings and suggestions, as well as the expectation of success must come from the prior art and not the applicant's disclosure. *See, In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Applicants assert that the references by Sommer and Xue, when viewed either alone or in combination, do not suggest the claimed invention. The reference by Sommer *et al.* does not teach or suggest a method of or composition for treating a nerve disorder mediated by nucleus pulposus in a mammal as discussed with the Examiners during the interview.

The Patent issued to Xue *et al.* fails to cure the defects inherent to the reference by Sommer *et al.* A reference must be read for what it teaches on a whole and not selectively. Moreover, prior art references must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention. *Akzo N.V. v. International Trade Commission*, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986). Xue *et al.* teach the use of matrix metalloproteinase inhibitors for the treatment of rheumatoid arthritis, osteoarthritis and similar pathological conditions (*see,* col. 9, ll. 35-38). *See also,* col. 9, ll. 43-46 (". . . it is meant an amount of a compound of the present invention effective to inhibit stromelysin or to treat symptoms of osteo-or rheumatoid arthritis in a host."). Additionally, of the laundry list of inflammatory diseases provided, none of them include nerve disorders let alone nucleus pulposus mediated nerve disorders (*see,* col. 37, l. 67 to col. 38, ll. 13). Accordingly, the reference by Xue *et al.* alone does not teach or render obvious the claimed invention and cannot cure the defects inherent to Sommer when combined.

B. Wang in view of Xue

Claims 1-48 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Wang *et al.* in view of Xue *et al.* The Office Action sets forth that it would have purportedly been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the methods disclosed in Wang *et al.* to treat neurological conditions resulting from spinal cord injury by inhibiting TNF as described by Xue *et al.* One of ordinary skill in the art would have purportedly been motivated with reasonable expectation of success to modify the methods of Wang *et al.*, because Xue *et al.* purportedly teach the treatment using pharmaceutical compositions containing a metalloproteinase inhibitor and the various forms of administration into mammal including humans to inhibit the production of TNF to treat inflammation.

The test for obviousness is provided above in section (A). Applicants again assert that the references when viewed alone or in combination do not teach the claimed invention for at least the following reasons. Xue when viewed alone does not suggest the claimed invention as discussed above. The Xue *et al.* reference also fails to cure for the same reasons the defects inherent to Wang.

Wang fails to support a *prima facie* case of obviousness alone or in combination with Xue. Again, Wang must be read for what it teaches as a whole. By the Office's own admission, Wang *et al.* do not explicitly recite the administration of TNF-α inhibitor to a mammal to inhibit the TNF production and to treat nerve disorders let alone those mediated by the nucleus pulposus. (Office Action, page 10, lines 1-3). Accordingly, Wang therefore cannot teach any mode of administration of inhibitors (*e.g.*, intravenous). These defects are not cured by Xue for the reasons presented above.

Additionally, Wang presents two contradictory statements, at least. First, "[o]ver-production of TNF may be detrimental to the CNS, as TNF stimulates the proliferation and hypertrophy of astrocytes. . . ." (*J. Neuroimmunol.*, 69: 151-6, 151, right col.). Second, "...TNF may be involved in the regeneration and recovery after CNS injury when an optimal concentration is present." *Id.*, at 152, first col. Therefore, on the one hand it is detrimental and on the other hand, TNF may be beneficial to the subject suffering from a CNS injury. This disharmony of scientific thought is further propounded upon by the authors in their conclusion as follows:

> This temporal pattern suggests a possible relationship between TNF and this polypeptide in the injured spinal cord. Furthermore, TNF often influences the synthesis and function of other cytokines resulting in a complex cytokine network. Together with the molecules, TNF may play a role in the postinjury process. However, confirmation of the role of this and other cytokines in the postinjury processes requires more experiments. *Id.*, at 155, left col.

Accordingly, the primary reference ("Wang") cannot suggest the claimed invention given the uncertainty of TNF's role in view of the other cytokines, as discussed by the authors. Wang alone does not suggest the claimed invention and Xue cannot cure its defects. Therefore, no *prima facie* case of obviousness has been adduced, and the rejection under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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